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Inflammatory Parental Nutrition-associated Disease

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DISSERTAÇÃO DE CANDIDATURA AO GRAU DE MESTRE EM MEDICINA
CASE REPORT

Inflammatory Parental Nutrition-associated Disease

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LIST DE ABREVIATIONS

AIH – Autoimune Hepatitis

ALT – Alanine transaminase

AST – Aspartate transaminase

AZA – Azathioprine

BBS – Bowel bypass syndrome

HPN – Home parental nutrition

IFLAD – Intestinal failure-associated liver disease

MTX – Methotrexate

PN – Parental Nutrition

PN-MBD – Parental Nutrition-associated Metabolic Bone Disease

PTH – Parathyroid hormone

RA – Rheumatoid arthritis

SLZ – Sulfasalazine

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I. INTRODUCTION

Long-term parenteral nutrition is an essential therapy for patients with intestinal failure. The major causes of intestinal failure are short bowel syndrome, Crohn's disease, pseudo-obstruction, radiation enteritis and enterocutaneous fistulae[1]. Despite its noticeable benefits, long-term parenteral nutrition (PN) is associated with significant complications such as infection, inflammation, liver dysfunction, bacteria translocation, metabolic and electrolyte disturbances, whose physiopathology is not well understood mainly due to scarce experience. We present a case report of a 42-year-old woman, exclusively under total home parenteral nutritional (HPN) for 10 years, after being subjected to subtotal enterectomy plus colectomy due to intestinal ischemia, that later developed seronegative arthritis, liver dysfunction and metabolic bone disease. The authors discuss the diagnostic possibilities and physiopathology underlying the patients' clinical manifestations, as well as its management challenges.

II. CASE DESCRIPTION

A previously healthy 32-year-old woman was admitted to the emergency department in 2008 with acute abdomen, three weeks following her first child's uncomplicated eutocic delivery. The exploratory laparotomy uncovered a midgut volvulus with infarction of the small intestine, cecum and ileocecal valve, leading to a subtotal enterectomy (only the duodenum and 2 cm of jejunum was left) and colectomy of the cecum and a portion of the ascending colon. Inflammatory bowel disease was excluded. The resulting intestinal failure lead to long-term PN requirement. Since then, several complications have developed, most of them associated with the long-term HPN therapy.

Regarding the constitution of the HPN bag, it includes: Nutriflex Lipid Special®, Adamel®, Vitalipid®, Soluvit®, Glycophus, magnesium sulphate, zinc and calcium gluconate.

Despite total PN, the patient sustained oral consumption of food regularly. Some episodes of abdominal pain with watery diarrhea were often reported. A recent colonoscopy progressed to duodenum and revealed no relevant findings.

Several episodes of catheter-associated infections and septicemia have occurred, justifying hospital admission for parental antibiotics. However, no infectious episodes have occurred in the last 7 years.

Cholestatic jaundice with subsequent coagulopathy and dyslipidemia was also detected in the first months of HPN. Both alanine transaminase (ALT) and aspartate transaminase (AST) were consistently high since 2008, although currently normal. Four months after total HPN initiation, a liver biopsy showed cholestasis, periportal space bile thrombus, fibrosis, formation of septa and proliferation of new ducts with lymphoplasmocytic inflammatory infiltrate in the periportal space and focal signs of necroinflammatory activity. No significant steatosis was present. Viral and autoimmune hepatitis were excluded.

Progressive osteoporosis has been detected in densitometries since 2009 (lower spine T increased from -2.5 to -3.3; femur T -0.9 to -2.6) despite parenteral ergocalciferol and paricalcitol and high doses of oral cholecalciferol. Serum levels of 25-hydroxivitamin D are consistently low or undetectable since 2008. In 2015, she had multiple osteoporotic vertebral fractures (in D5, D12, L1, L2, L3 and L4) with aggravated lower back pain. Kidney function, serum total calcium and phosphorous levels have always been normal. Parathyroid hormone (PTH) serum levels were at first low, but since the end of 2014 they spiked to approximately twice the upper limit (100-160; N:15-65), with no possible relation with the dosing of paricalcitol. Parathyroid scintigraphy excluded primary pathology of the glands.

In April 2014, the patient presented with symmetric polyarthritis of the small and large joints and morning stiffness lasting for more than 2 hours, limiting the patient's ability to prepare the PN bag. A magnetic resonance of the hands imaging showed wrists synovitis with no proliferation or bone erosions. Laboratory tests revealed a persistent inflammatory state: long-term normocytic normochromic anemia (which has normalized in 2015); isolated hyperferritinemia since 2008 (median=1757; reference values=2.20-178ng/mL); erythrocyte sedimentation rate (median=26; reference values= 0-19 mm/h) and C-reactive protein (median=1.03; reference values= 0-5.0 mg/L) have always been slightly elevated.

The patient is seronegative for rheumatoid factor, anti-citrullinated protein, anti-neutrophils cytoplasm (ANCA), anti-Saccaromyces cerevisiae (ASCA), anti-nuclear, anti-double stranded DNA, anti-Sm, anti-U1 RNP, Anti-SS-A/Ro and Anti-SS-B/La autoantibodies. Immunoglobulin G level is high (2237mg/dL); serum complement C3 and C4 levels are normal.

A partial response was obtained with 10mg/morning of prednisolone, and later azathioprine (AZA) 50 mg/day was added (primarily absorbed in the stomach, jejunum and cecum). However, since there was insufficient clinical response, AZA

was switched for methotrexate (MTX) 10-15 mg subcutaneous/week with improvement but no complete remission. In order to reduce MTX dosing (due to liver profile and relative contraindication) sulfasalazine (SLZ) (500mg+500mg) was introduced. The patient's remarkable clinical response to SLZ, allowed the steroid dose tapering for the first time.

III. DISCUSSION BASED ON LITERATURE REVIEW

i. Parental Nutrition

The use of PN is a well-established therapy that results in long-term survival of patients with intestinal failure. Although the value of this life-sustaining treatment is clear, there are potential negative outcomes associated with this therapy. Complications can be infectious, mechanical, or metabolic, although it is unclear if they are due to the PN treatment per se or associated to the diseases that lead to the intestinal insufficiency. In general, however, the pathogenesis of PN associated diseases is currently considered to be multifactorial and a patient-dependent phenomenon (cause and extent of short bowel syndrome, bacterial translocation, and nutritional factors)[(2)].

Data on patient outcomes has been difficult to collect, as there is no prospective database of patients on HPN. Mullady DK et al refers to a 20-year experience database at the Mayo Clinic with 255 HPN patients in 1999. In this study, the overall probability of the 5-year survival during HPN was 60%. Probability of survival correlated with the underlying disease process and with age – young patients had an improved survival rate. Death from TPN-related complications is generally rare but can occur from catheter-related sepsis [(1)].

ii. Inflammation and immune function in HPN patients

One hypothesis to explain PN-associated disease is that a permanent chronic inflammatory status exists among these patients, based on animal studies and few human studies confirming that HPN leads to a low-level, chronic, inflammatory response. The lack of significant small intestinal mass (as in short bowel syndrome) or the absence of small intestine stimulation through normal enteral feeding could lead to the increase level of inflammation or immune impairment observed on HPN

patients. Alternatively, component(s) of the PN solution could lead to these results, and each condition could interact and exacerbate the other[3].

iii. Catheter-related infections

Catheter-related infection is the most common complication and major cause of morbidity among patients on HPN; it accounts for approximately 70% of HPN-related hospitalizations[1]. The occurrence of several episodes of sepsis on PN patients increases the possibility of metastatic infection from the primary parenteral nutrition line. Our patient had several episodes of catheter-associated infections and bacteremia; however, these have not occurred in the last 7 years, making it an unlikely explanation for the patient's most recent clinical manifestations.

iv. Hepatobiliary disorders

Intestinal failure-associated liver disease (IFALD) is the hepatic dysfunction that occurs secondary to intestinal failure in the presence of PN. In adults, the major types of total HPN-associated liver disease are intrahepatic cholestasis, steatosis (microvesicular and macrovesicular), steatohepatitis and cholecystitis; however, overlap can exist.

Although the patient's liver histologic findings were compatible with autoimmune hepatitis (AIH), the biopsy was performed early after several metabolic and inflammatory events, and beside hypergammaglobulinemia, no other findings were compatible with AIH and no change occurred with immunosuppressive treatment.

Persistent inflammation and immune activation have been suggested as contributors to chronic cholestasis in patients who receive HPN[4]. Although arthritis has not been described associated with IFLAD, inflammation establishes a possible relation between them. In one study, a subset of patients with extreme short bowel

without an associated inflammatory disorder, had no evidence of liver disease after an average of 13.6 ± 6.7 years of HPN[5]. This suggest that it is the presence of an associated underlying inflammatory disorder, rather than simply the remaining length of small intestine, that poses the greatest risk for the development of end-stage liver disease.

v. Metabolic Bone Disease

The bone metabolism disturbances associated to PN have been extensively described. It manifests as either osteomalacia with excessive organic bone matrix, but deficient calcification or osteoid tissue, or osteoporosis with decreased bone mass characterized by an increase in the ratio of bone formation, and a normal ratio of mineral to organic constituents. A combination of osteomalacia and osteoporosis may also be observed. It is unknown how long a patient must be on total PN before bone disease becomes evident[6].

Most cases of PN-associated metabolic bone disease (PN-MBD) relate to abnormalities in the handling of calcium, phosphorus, vitamin D and K, as well as underlying medical conditions such as Crohn's disease. Patients with PN-MBD may present with bone pain and bone fractures with minimal or no trauma; but, most are asymptomatic. Biochemical parameters associated with bone formation and mineralization are often normal. In some cases, an elevation in urinary calcium, and an increase in serum calcium, phosphorous and alkaline phosphatase may occur[7].

An iatrogenic adynamic bone disease related to excessive paricalcitol administration is a hypothesis to be considered. The patients underlying inflammatory state also contributes to this metabolic bone disease.

Our patient presents vitamin D deficiency and hyperparathyroidism despite receiving high doses of oral cholecalciferol, paricalcitol IV and ergocalciferol in the

PN bag. Paricalcitol, an analog of 1,25-dihydroxyergocalciferol, acts as an agonist at the vitamin D receptor and thereby lowers parathyroid hormone levels in the blood. However, the patient's PTH does not seem to suppress despite high doses of this drug. Paricalcitol is traditionally prescribed to treat secondary hyperparathyroidism in chronic kidney disease patients; its efficacy and side-effects in patients under HPN is unknown.

The absence of bone biopsy, the persistent inflammatory state and the maintenance of oral intake by the patient makes its interpretation rather complex.

Systemic inflammation and chronically high levels of circulating cytokines interact with bone through multiple pathways, synergizing to produce profound net bone loss. This interaction between inflammation and bone loss, typically observed in patients with rheumatoid arthritis (RA), clinically reflects the molecular and cellular interactions between the immune system and the bone, also known as osteoimmunology. This makes the initial hypothesis of an association of long-term PN use with chronic inflammatory sequelae and a potential for associated immune dysfunction one that must be considered.

vi. Joint inflammatory disease

Following jejunoileal bypass, rheumatic manifestations develop in up to 20% of cases. When Dicken and Seehafer reported for the first time in 1979 a condition named bowel bypass syndrome (BBS) (characterized by recurrent episodes of fever, malaise, nonerosive polyarthralgia or arthritis, and the development of skin lesions), one of the most likely hypothesis was bacterial overgrowth in a blind loop syndrome[8].

The complex interactions between the gut microbiota and the modified intestinal environment in PN patients is crucial for understanding the joint-gut

dysbiosis axis, which has been described particularly in patients with Inflammatory Bowel Disease. The PN-associated proinflammatory state within the intestinal epithelium and resulting loss of the epithelial barrier function promotes the susceptibility of the epithelial barrier to enteroinvasion and translocation of microbiota-derived products. There is increasing evidence that the PN-dependent state leads to primary significant shift in the makeup of the intestinal microbiome[9]. To date, limited data regarding the impact of PN on the human intestinal microbiome is available.

Mechanisms by which intestinal microbiota contribute to initiation or severity of autoimmunity are varied. Recently, investigators have focused on the gut microbiota, which is thought to be an environmental agent affecting the development RA. A study by Pianta *et at* provides new evidence that the pathogenesis of RA may involve molecular mimicry[10]. Molecular mimicry is one mechanism by which dysbiosis can impact the pathogenesis of autoimmunity. Genetic factors may affect the composition of the microbiome; dysbiosis may perturb the poise of the immune system; and inflammation may lead to dysbiosis. The interplay between host and organism is thus likely to be complicated and dynamic.

Inflammation is a plausible explanation for the patient's clinical manifestations as shown by analytic findings and the clinical response to immunosuppression. The association between bone disease and arthritis is well established in RA but this patient presents a seronegative non-erosive arthritis, so this hypothesis in unlikely. The inflammatory etiology for her arthritis seems to be the most probable, although the trigger of this process is not known.

The previous intestinal surgery by itself could cause a blind-loop syndrome but the gap between surgery and the arthritis is too long. It could be a BBS, through

bacterial overgrowth in the remnant intestine, but no skin lesions have been found. Another hypothesis is a pre-existent underlying subclinical process that could be having clinical manifestations just now. Inflammatory Bowel Disease, like Crohn's Disease, could aggregate and explain the clinical manifestations found, having the patients shown remarkable response to SLZ. However, it seems unlikely due to the normal colonoscopy, but further investigation is needed. SLZ is an intestinal immunomodulator used to treatment of Inflammatory Bowel Disease, as well as other inflammatory arthritis; we could hypothesize that the remarkable clinical response to SLZ supports the hypothesis of underlying intestinal dysbiosis as a trigger for an autoimmune process.

vii. Limitations of the case

To clarify the bone disease etiology, a bone biopsy would be necessary. Additionally, microbiota characterization of the intestinal population would be of great value but very few laboratories perform it and there is scarce data for its interpretation. A longer follow-up time will also be of the upmost importance, as further symptomatic manifestations may clarify the etiology of the underlying disease.

IV. CONCLUSION

Long-term parenteral nutrition follow-up is limited, so the knowledge of associated diseases and complications are still in early stages of being described and understood. It is important to remember that PN is an unphysiologic route of nutrient supply that bypasses the gastrointestinal tract and portal system, making the effects of continuously administering of these nutrients directly into venous blood largely unknown. We described a clinical case of a female patient submitted to long-term HPN and several associated co-morbilities such as bone associated disease and hepatic disorder. More recently, a less understood arthritis developed, resistant to AZA and largely responsive to SLZ. A common etiopathological explanation to aggregate most of the patient's manifestations was hypothesized.

This case report will shed new light on the possible pathogenic effects of long-term exposure to this life-saving therapy. Since there is limited knowledge regarding the long-term impact and management of HPN patients due to lack of research in this area, additional studies are required.

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